abbreviation disclosed in the chart on page 19. Correction at pages 8 and 14 is requested for two other obvious spelling errors. The amendment requested at page 12 is to provide a more conventional designation of the disclosed analysis on the Applied Biosystems gas phase sequencer.

The Formal Restriction Requirement

Restriction has been required to one of the following inventions:

Group I. Claims 1-3.
Group II. Claims 4-7.

Applicant respectfully traverses the requirement for restriction for reasons as follows, but herewith confirms the provisional election of the Group II, Claims 4-7.

Although the protein Claims 1-3 may be patentably distinct from the DNA Claims 4-7, it would constitute an unnecessary, unreasonable and burdensome requirement to split this application into two parts. Since the DNA sequences of Claims 4-7 encode the protein sequences of Claims 1-3, it would be most convenient, efficient and logical, and would result in a savings of cost and time to both the PTO and applicant to have the two Groups I and II examined in one application. It is well-known that the PTO has a large backlog of biotechnology applications. To require a separate Divisional application for the non-elected Group I claims could only add to this backlog. See the comments of Rep. Ron Wyden on this problem in BioPharm., June 1991, pages 20-21, copy attached hereto.

Since the DNA sequences and the proteins which they encode are inextricably related to each other, the Examiner's search on the DNA sequences would logically include a search on the protein sequences. Applicant is not claiming random DNA sequences in Claims 4-7 which have no applicability to a protein but, rather, sequences which encode particular proteins as recited in Claims 1-3.

The requirement to split this application into two parts also would cause inconvenience to scientists and other members of the public who may be interested in the invention. They would have to search two patent files instead of one file for the patent results on a DNA and protein that are inextricably related to each other. It is not likely that anybody would be interested solely in a random DNA sequence in a vacuum without consideration of the protein that it encodes. If applicant had disclosed merely a random DNA sequence without also disclosing a particular protein sequence the application is not likely to have been very useful to scientists and other members of the public without considerable additional effort on their part.

Nevertheless, applicant herewith provisionally elects to prosecute the Group II, Claims 4-7, invention in this application as required by the Examiner's action.

The Rejection Under 35 U.S.C. §101

Claims 4-7 have been rejected under 35 U.S.C. §101 on the alleged ground that the claims are directed to non-statutory subject matter. This rejection is traversed for reasons as follows.

First of all, in accordance with long existing patent law, already acknowledged by the Examiner, an article of manufacture or composition of matter occurring in nature can be considered patentable if given a new form, quality, property, or combination not present in the original article existing in nature. See, e.g., Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 76 USPQ 280 (1948); American Fruit Growers v. Brogdex, 283 U.S. 1, 8 USPQ 131 (1931); and Ex parte Grayson, 51 USPQ 413 (Bd. App. 1941). This legal doctrine has recently been reiterated by the PTO Notice of the Assistant Secretary and Commissioner, 1077 OG 24, April 21, 1987.

In line with the foregoing general rule of law, it has also been held that where the claimed product is the result of processes of extraction, concentration, or purification of natural materials to thereby make a usable product out of a hitherto substantially unusable product, a patent on the product may be granted. This is illustrated, for example, by the case of Merck & Co. Inc. v. Olin Mathieson Chemical Corp., 253 F.2d 156, 116 USPQ 484 (4th Cir. 1958). In said case, the purification of the active principle in a natural ferment resulted in a patented composition where the natural ferment was quite useless but the purified product had great medicinal and commercial value.

While applicant's heparin-binding growth factor or HBGF-8, may have existed in nature, it is claimed herein in a new form and quality not present in the original substance in nature. The exhaustive detailed steps of concentration, purification and isolation required to produce the HBGF-8 molecule by recombinant DNA procedures is fully disclosed in the application, especially in the detailed description at pages 8-18.

The DNA cloning in the present case was done by humans, not by nature. Without this work by humans, the HBGF-8 would still be in its natural form virtually unavailable and non-reproducible for use as a potential therapeutic growth factor. The naturally occurring state of the claimed HBGF-8 is in the bovine uterus and human placenta. None of these crude materials would be useful as a heparin-binding growth factor, and the Examiner has not presented any basis for concluding that these naturally occurring sources of HBGF-8 would be useful as a heparin-binding growth factor as is the highly purified HBGF-8 of the present invention.

In accordance with the Examiner's helpful suggestion at the top of page 5 of the office action to overcome the rejection under 35 U.S.C. §101, applicant herewith amends Claims 4-7 by insertion of the language "purified and isolated." Accordingly, withdrawal of the rejection under 35 U.S.C. §101 is respectfully requested.

The Formal Objection Under 35 U.S.C. §112

The specification has been objected to under 35 U.S.C. §112, first paragraph, on the alleged ground that applicant has failed to provide an adequate written description of the invention, an enabling disclosure and the best mode. This objection is traversed for reasons as follows.

First of all, the starting biological materials for isolating the heparin-binding growth factor (HBGF-8) protein and cDNA are bovine uterus and human placenta as specifically disclosed at page 3, lines 2-4, and at page 4, lines 5-6 and 13-15. These biological materials are readily available by ordinary surgical procedures in bovine and human sources which are

abundantly and widely accessible throughout the world. Bovine uteri can be obtained commercially from numerous slaughter houses and human placenta can be obtained from many hospital laboratories. No unique bovine or human strain is required for carrying out the invention. No screening of numerous bovine uterii or human placenta are required to find a suitable source of starting material. Moreover, human placenta cDNA libraries are available from commercial supply houses. Thus, the rules which require the deposit of unique hybrid or mutant strains of microorganisms and host cells which are not widely disseminated or difficult to find and isolate or mutate have no bearing to the present case.

Secondly, the procedures for isolating and purifying the HBGF-8 protein and cDNA from the bovine uteri and human placenta biological starting materials are fully disclosed in the detailed description of the invention at pages 8-18. Thus, the person skilled in the art of protein purification from natural sources and recombinant DNA procedures can readily and easily reproduce the invention from the written description. The Examiner has provided no factual or legal justification to require applicant under these circumstances to undergo the costly and burdensome requirement of making a public culture deposit of materials used or made according to the claimed invention.

Thirdly, applicant has disclosed the full and complete sequence of 168 amino acids of the HBGF-8 protein and the full and complete sequence of 995 nucleotides of the HBGF-8 cDNA which encodes said protein. These sequences are briefly described at page 4, lines 1-25, and they are fully and completely described at pages 5-7. Thus, the person skilled in the art could readily and routinely reproduce these sequences by conventional

techniques for protein and nucleotide sequencing merely by reference to these disclosed sequences even if the aforesaid disclosure on the procedures for isolating and purifying the HBGF-8 from bovine uteri and human placenta were not also disclosed. The biotechnology literature is profuse with information on how to readily and routinely synthesize proteins and genes from known sequences. Illustratively, applicant calls the Examiner's attention to the attached article by Dr. Mark Edwards, Head of Molecular Biology, British Biotechnology Laboratories, Amer. Biotechnol. Lab., pages 38-42, published November/December 1987, and especially the conclusion near the bottom of page 42, right-hand column, that:

> "Gene synthesis technology has developed to where the synthesis of genes from 500 to 2000 bp is rapid and routine (emphasis added)."

See also the attached three articles from Nature 332, 477-478 (1988), which briefly describe three well-known, commercially-available automated DNA sequencers.

Under the foregoing circumstances, there can be no valid justification for requiring applicant to make a culture deposit of the HBGF-8 gene. The quality of applicant's disclosure of the best mode is not so poor as to effectively result in concealment according to the test set forth In re Sherwood, 204 USPQ 537 (CCPA 1980), cited by the Examiner. The best mode is clearly and fully disclosed by virtue of the disclosure of the full DNA and protein sequences and their method of obtaining. Accordingly, it is respectfully requested that the objection to the specification under 35 U.S.C. §112, first paragraph, be withdrawn.

The Prior Art Rejection

Claims 4-7 have been rejected under 35 U.S.C. §103 as being unpatentable over Bohlen (EP 326,075) or Rauvala (EMBO J., 1989) in view of Maniatis et al. This rejection is traversed for reasons as follows.

First of all, applicant's claimed HBGF-8 protein and DNA are purified and isolated from entirely different biological starting materials than used by Bohlen and Rauvala. Thus, on the one hand, applicant isolated and purified the HBGF-8 protein and cDNA from bovine uterus and human placenta; whereas, on the other hand, Rauvala isolated and purified his heparin-binding protein from rat brain, and Bohlen isolated and purified his heparin-binding protein from bovine brain (and also suggested rat and chicken brains). That is, both Bohlen and Rauvala emphatically teach the use of brain tissue as the source of their heparin-binding growth factors which is an entirely different tissue source than used by applicant. There is nothing in the four corners of either of these references which teaches or suggests the use of bovine uterus or human placenta as a source of obtaining the HBGF-8 of applicant. It is well-known that peptides and proteins isolated from brain cells generally are different molecules than peptides and proteins isolated from other types of cells. It is, therefore, erroneous to conclude ipso facto that applicant's HBGF-8 is the same as or obvious over the heparin-binding growth factors isolated by Bohlen and Rauvala.

Secondly, neither Rauvala nor Bohlen disclose sequences other than a partial NH_2 terminal sequence. Thus, they are not enabling disclosures of applicant's claimed HBGF-8 protein and cDNA. However, Rauvala subsequently disclosed his full sequence in a publication cited to the Examiner on January 7, 1991, namely J. Biol Chem. 265, 16721-16724 (1990). Although the latter reference is not prior art, it can be seen from the fully disclosed rat brain-derived sequence of Rauvala that both the bovine uterus- and human placenta-derived sequences of applicant are different from the rat brain sequence of Rauvala. This confirms that applicant's invention relates to a different protein and DNA than disclosed by Rauvala. Applicant attaches hereto an enlarged copy of the Rauvala sequence of FIG. 2 on page 16722, in which applicant's amino acid residues and nucleotides which differ from Rauvala are highlighted. In applicant's HBGF-8 from human uterus the sequences differ at amino acid residues 98, -13, -30 and -31. In applicant's HBGF-8 from bovine uterus the sequences differ at amino acid residues -13, -29, -30 and -31. Thus, the Rauvala rat brain protein has Asp at residue 98, whereas applicant's human uterus-derived HBGF-8 has Glu at the corresponding residue (residue 130 in applicant's sequence). Likewise, Rauvala's rat brain protein has Ser-Ser in residues -30 and -31, whereas applicant's human uterus-derived HBGF-8 has Gln-Ala at the corresponding residues (residues 2 and 3 in applicant's sequence). Since applicant's claimed cDNA sequence includes coding for the signal peptide, applicant's amino acid numbering starts with the NH_2 terminal Met as number +1.

The Bohlen reference discloses only the first 19 residues of his NH_2 terminal sequence and no signal sequence is provided. Thus, no full comparison can be made with applicant's sequence. However, since the Bohlen protein is derived from brain tissue rather than uterine tissue, it is believed to be the same as the

Rauvala protein rather than applicant's protein. In any event, Bohlen does not provide any disclosure whatsoever of the DNA sequence as claimed by applicant and, moreover, there is no basis to conclude that applicant's DNA sequence which is derived from human uterus is obvious from the Rauvala rat brain DNA sequence combined with the Bohlen teachings on the human brain heparin-binding protein.

Maniatis is nothing more than a general text on cDNA cloning methodology. It teaches nothing whatsoever concerning applicant's claimed HBGF-8 protein or cDNA. Applicant's claimed invention does not reside in the methodology of cDNA cloning. Such methodology is conventional and not the basis of the claimed invention. Rather, applicant's invention in Claims 4-7 resides in unique sequences which not only are not taught by Maniatis, but also are different from the DNA sequences of the other references.

In view of the amendments to the specification and claims complying with the Examiner's formal requirements, together with the traverse of all other rejections and objections, it is submitted that all of applicant's claims are now allowable. Allowance thereof is courteously solicited.

The Notice of Patent Drawings Objection regarding informal drawings is noted. In accordance with MPEP §608.02(b), applicant requests permission to delay filing of the formal, corrected drawings until receipt of a Notice of Allowability (PTOL-37).

Respectfully submitted,

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Enc.

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